Capecitabine monotherapy and in combination with immunotherapy in the treatment of metastatic renal cell carcinoma

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This prospective trial aimed to evaluate the therapeutic effects and systemic toxicities of capecitabine monotherapy and capecitabine treatment combined with biological response modifiers in patients with metastatic renal cell carcinoma. Fifty-four patients suffering from metastatic renal cell carcinoma progressing under first-, second- or third-line treatment entered the trial. Capecitabine was given orally at a dose of 2500 mg/m^2 daily divided into two doses for 14 days, followed by a 7-day rest in the monotherapy as well as in the combination treatment. This schedule was repeated in 3-week cycles. The combination therapy consisted of capecitabine and an immunotherapy treatment, which consisted either of interferon (IFN)-γ1b (100 mg/day) administered consecutively 5 times weekly during weeks 1 and 2, and recombinant interleukin (IL)-2 (4.5 MU/day) administered on 4 consecutive days during weeks 3 and 4, every 6 weeks, or IFN-α (6 MioIE/day) administered 3 times a week. Fifty-two patients are now evaluable for response and 54 patients for toxicity. We observed a partial response to treatment in five patients (9.6%), minor response in five patients (9.6%), stable disease in 32 patients (61.6%) and only 10 patients (19.2%) showed continued disease progression despite treatment. Outpatient capecitabine was well tolerated. We did not observe any WHO grade IV toxicities. We conclude that capecitabine monotherapy and capecitabine treatment in combination with biological response modifiers appear to be effective regimens with favorable toxicity profiles in patients with advanced renal cell carcinoma. Capecitabine monotherapy seems to be superior than the combination treatment because of its easier application form.
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Introduction

Renal cell cancer is still a frequent cause of cancer morbidity and mortality all over the world [1]. Localized disease is potentially curable using nephrectomy as therapy, but in approximately two-thirds of patients, metastatic disease will develop, which then turns out to be mostly chemotherapy resistant [2]. The possibility to achieve objective and durable remissions using biological response modifiers alone [3–5] or in combination with cytostatic agents remains poor as well [6–8]. Currently, combined therapy with biological response modifiers is considered standard first- and second-line therapy in patients with metastatic renal cell carcinoma [4,9,10].

Capecitabine is an orally administered fluoropyrimidine carbamate, activated by a three-step enzymatic conversion to the cytotoxic agent 5-fluorouracil (5-FU). After oral administration, capecitabine is rapidly absorbed as an intact molecule [11,12].

The rationale for developing this prospective study was the results of Miwa *et al.* [11], who demonstrated that kidney cancer cell lines contain a considerable amount of thymidine phosphorylase, a key enzyme for the conversion from capecitabine and its metabolites to intracellular 5-FU. Our study group [13] could demonstrate significant activity of capecitabine in the treatment of patients with advanced renal cell carcinoma failing immunotherapy. Similar results were reported by Oevermann *et al.* [14] adding capecitabine to standard biological response modifiers in the first-line treatment of patients with advanced renal cell carcinoma.

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Based on these results we conducted a prospective clinical single-institution evaluation of capecitabine monotherapy and capecitabine treatment combined with biological response modifiers to determine, as the primary objective, therapeutic response and systemic toxicity. The second goal was to demonstrate a possible positive effect of the combination therapy in patients with advanced renal cell carcinoma. Additional goals of this study were to determine time to progression (TTP) and overall survival of this patient population.

Patients and methods

Patients

The protocol was approved by the local ethics committee. Fifty-four patients with histologically confirmed metastatic renal cell carcinoma were accrued in this prospective clinical trial between May 1998 and January 2002.

Criteria for inclusion were as follows: histologic proof of metastatic renal cell carcinoma in advanced state, age 19–80 years, Karnofsky performance status $> 70\%$, life expectancy of > 3 months, adequate organ function as defined by WBC count $\geq 3500/\mu l$, platelet count $\geq 100\,000/\mu l$, hematocrit $\geq 30\%$, serum bilirubin and creatinine $\leq 1.25 \times$ upper limit of the institution's normal range, and informed consent. Patients with controlled brain metastases after surgical resection or γ-knife treatment were also eligible. Patients were not allowed to be under concurrent cytostatic treatment due to another malignancy. Other contraindications included pregnant or nursing women and uncontrolled infection. Adequate contraception was mandatory.

For staging evaluations, computed tomography of the chest, abdomen and brain, as well as a bone scan were required. X-ray studies of selected osseous segments were performed when clinically indicated. Patients had at least one neoplastic lesion bidimensionally measurable by physical examination or instrumental studies, which should be ≥ 1 cm.

Treatment plan and patient evaluation

All treatments were administered in an outpatient setting. Capecitabine was given orally at a dose of 2500 mg/m^2 daily divided into two doses for 14 days, followed by a 7-day rest in the monotherapy as well as in the combination treatment. This schedule was repeated in 2-week cycles. The combination therapy consisted of capecitabine and an immunotherapy treatment, which consisted either of interferon (IFN)-γ1b (100 mg/day) administered consecutively 5 times weekly during weeks 1 and 2, and recombinant interleukin (IL)-2 (4.5 MU/day) administered on 4 consecutive days during weeks 3 and 4, every 6 weeks, or IFN-α (6 MioIE/day) administered 3 times a week.

Re-evaluation of patients' tumor status was performed with computed tomography of the chest and abdomen with additional work up if indicated every 3 cycles of therapy according to WHO criteria. Complete response (CR) was defined as the disappearance of all measurable disease for a minimum of 8 weeks. Partial response (PR) was defined as 50% or more reduction in sum of products of the greatest perpendicular diameters of measurable lesions, no increase in lesion size and no new lesions. Minor response (MR) was defined as 25–50% decreased tumor size. Stable disease (SD) was defined as less than 25% decrease and less than 25% increase without the appearance of new lesions for a minimum of 9 weeks (3 cycles of therapy). Progressive disease (PD) was defined as a greater than 25% increase in tumor size or the appearance of new lesions.

Monitoring of serum chemistry and blood cell count was performed prior to each capecitabine cycle of therapy in 3-weekly intervals in the monotherapy as well in the combination therapy. In case of hematotoxicities necessitating a delay of starting orally application of capecitabine, blood counts were performed in weekly intervals. Patients were advised to report any adverse event, especially body temperature more than 37.6°C during treatment cycles. Toxicity was evaluated according to WHO criteria. Hand–foot syndrome WHO grade II and bad tolerability of the patient led to a 25% dose reduction. WHO grade III toxicity led to a 25% dose reduction and if symptoms persisted to a 50% reduction. If toxicity did not improve or WHO grade IV toxicity occurred, therapy was discontinued.

Statistical analysis

Time to progression (TTP) was defined as the interval from the first day of capecitabine application until tumor progression. If a patient died without restaging for documenting disease status, the TTP was measured to the first day of clinical deterioration. Survival time was measured from the first day of capecitabine application until death. Data were analyzed as of 28 February 2002. The distribution of TTP and time to death were estimated using the Kaplan–Meier product-limit method [15]. To test the difference between survival curves the log-rank test was used. p values less than 0.05 were considered to indicate statistical significance. Toxicity was evaluated according to the WHO criteria and was recorded per patient as the worst episode that appeared during a treatment cycle.

Results

Fifty-four patients (female/male: 14/40) suffering from metastatic renal cell carcinoma were included in this evaluation. All patients had clear cell cancer. Median age was 59.5 years (range 45–79 years) and median observation time was 10.5 + months (range 3–50 + months).

Table 1 lists the characteristics of the 54 patients included.

Thirty-eight patients with progressive disease after previous first-, second- or third-line treatment with biological response modifiers ± cytotoxic chemotherapy received capecitabine as monotherapy. Twenty-five patients (66%) received this therapy as second-line treatment. Four of these patients failed single-agent immunotherapy treatment and the other 21 patients failed combined immunotherapy treatment. Thirteen patients (34%) received this therapy regimen as third-line therapy. Out of these 13 patients, first-line therapy consisted of single-agent immunotherapy in five patients and of combined immunotherapy in eight patients. Second-line treatment consisted of single-agent immunotherapy in five patients, combined immunotherapy in four patients and single-agent immunotherapy combined with a cytotoxic agent in four patients, respectively. The time interval from the first occurrence of metastases to the start of capecitabine monotherapy was median 13 months (range 5–79 months) in patients receiving this therapy regimen as second-line treatment and median 23 months (range 9–91 months) in the third-line treatment group.

Table 1 Patients characteristics

Characteristics	Patients
Entered	54
Sex	
male	40
female	14
Karnofsky performance index	90–100%
Age (years)	
median (range)	58 (47–76)
No. of treatment cycles of capecitabine	466
all patients: median (range)	6 (3–36)
CAP monotherapy	
second-line: median (range)	7 (4–36)
third-line: median (range)	7 (3–27)
CAP combination therapy	
CAP + IFN-γ/IL-2 s.c.: median (range)	5 (3–21)
CAP + IFN-α: median (range)	3 (3–11)
Tumor nephrectomy	
yes	54
no	0
Histology	
clear cell	54
granular cell	0
spindle cell	0
sarcomatoid cell	0
CAP monotherapy	
second-line treatment	25
IFN-γ/GM-CSF/IL-2 s.c.	12
IFN-γ/IL-2 s.c.	8
IL-2 continuous infusion i.v.	3
IFN-γ s.c.	1
IFN-α s.c.	1
third-line treatment	13
first-line treatment	
IFN-γ/GM-CSF/IL-2 s.c.	5
IFN-γ/IL-2 s.c.	2
IFN-γ s.c.	2
IFN-α s.c.	4
second-line treatment	
IFN-γ/GM-CSF/IL-2 s.c.	1
IFN-γ/IL-2 s.c.	3
IL-2 continuous infusion i.v.	1
IFN-α s.c.	4
IFN-α s.c./vinorelbine i.v.	3
IFN-α/IL-2 s.c.	1
CAP combination therapy	
CAP+ IFN-α	4
second-line treatment	
IFN-γ/GM-CSF/IL-2 s.c.	3
IFN-γ/IL-2 s.c.	1
Metastatic sites	
visceral	42
bone	17
lymph nodes	18
cerebral	6
cutaneous	1
more than one metastatic site	43

Sixteen patients with metastatic renal cell cancer received capecitabine in combination with immunotherapy. Twelve patients were treated with capecitabine, IFN-γ1b and recombinant IL-2 as first-line therapy, and four patients received capecitabine in combination with IFN-α as second-line treatment after failing combined immunotherapy treatment. The time interval from the first occurrence of metastases to the start of capecitabine and IFN-α combination therapy was median 17 months (range 7–27 months).

Response and survival data

Out of all 54 patients, two patients (3.7%) entered the protocol, but were lost to follow-up with no evidence of PD or severe toxicity on initial therapy. Therefore these patients were not evaluable for response and survival, but were evaluable for toxicity. Five patients (9.6%) achieved a PR to treatment, five patients (9.6%) a MR, 32 patients (61.6%) a SD and only 10 patients (19.2%) showed continued PD despite treatment. Forty-two patients (80.8%) experienced a clinical benefit response (PR + MR + SD ≥ 6 cycles) of capecitabine mono- and combination therapy.

The sites of PRs to capecitabine treatment in the five patients were seen in the lung in three patients and in lymph node metastases in two patients. The sites of MRs were seen in the lung in four patients and in the liver in one patient. Thirty-six patients (69.2%) relapsed between 3 and 28 months, 33 patients (63.5%) were still alive, two patients (3.7%) were lost to follow-up and 19 patients (36.5%) had died. The median TTP was 5.5 months (range 3–39 + months) and the median survival time from the day of start of capecitabine monotherapy was 10.5 + months (range 3–50 + months).

The subgroup analysis for patients receiving capecitabine monotherapy as second- or third-line treatment revealed a clinical benefit response in 22 (91.7%) and eight (66.7%) patients, respectively. Lost to follow-up and therefore not evaluable for response were one patient

(4%) in the second-line and one patient (7.7%) in the third-line treatment. The subgroup analysis for the combination treatment revealed a clinical benefit response in nine (75%) patients treated with capecitabine in combination with IFN-γ and recombinant IL-2, and in three (75%) patients treated with capecitabine and IFN-α.

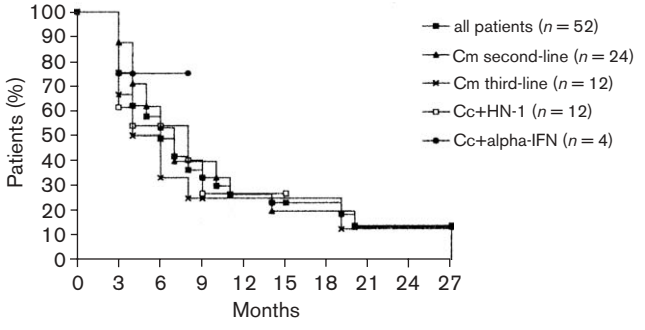
Median TTP was 6.5 (range 3–39 +) and 5 months (range 3–33 + months) in the monotherapy and 4 (range 3–15 +) and 4 + months (range 3–8 + months) in the combination treatment, respectively (Fig. 1). Kaplan–Meier analysis of the TTP revealed no statistical significance between the four subgroups ($p = 0.9286$).

Overall survival time was 11.5 (range 3–50 +) and 14.5 months (range 3–34 + months) in the monotherapy and 8 (range 3–16 +) and 6 + months (range 4–8 + months) in the combination treatment, respectively (Fig. 2). Kaplan–Meier analysis of the overall survival revealed no statistical significance between the four subgroups ($p = 0.7865$).

Toxicities

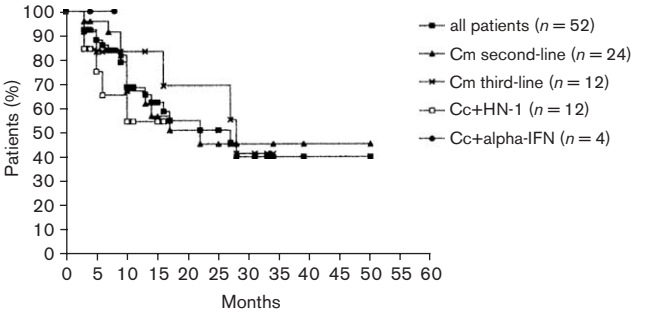
Capecitabine monotherapy was well tolerated and all patients completed the therapy on an outpatient basis. Fifty-four patients received a total of 466 cycles (median 6 cycles; range 3–36 cycles). Side-effects appearing in these 54 patients are shown together in Table 2, because of equal frequency and severity of toxicities in the mono- and combination treatment. No WHO grade IV toxicity was observed, and WHO grade III toxicity was hand–foot syndrome in five patients (9.3%), stomatitis in one patient (1.9%) and anemia in one patient (1.9%). WHO grade II leukocytopenia, anemia, hand–foot syndrome, nausea/vomiting, diarrhea, and infection were observed in one, one, nine, three, one and one patients, respectively. Renal impairment, cardiac toxicity, or allergic reactions were not observed in any of our patients. In all patients, treatment-related toxicities, especially in patients who received capecitabine monotherapy as long-term therapy, resolved after dose reduction or cessation of therapy. Hand–foot syndrome WHO grade II–III resolved after dose reduction within 6 weeks. No toxic death occurred. Dose reduction of 50% was necessary in seven patients (13%) because of WHO grade III toxicities and dose reduction of 25% was necessary in five patients (9.3%) because of hand–foot syndrome WHO grade II.

Fig. 1



TTP of 52 patients with advanced renal cell cancer receiving treatment with capecitabine monotherapy as second ($n=24$)- or third ($n=12$)-line therapy, or capecitabine in combination with either IFN-γ1b and recombinant IL-2 ($n=12$) or IFN-α ($n=4$). Cm, capecitabine monotherapy; Cc, capecitabine combination therapy; HN-1, IFN-γ1b and recombinant IL-2; alpha-IFN, IFN-α.

Fig. 2



Overall survival of 52 patients with advanced renal cell cancer receiving treatment with capecitabine monotherapy as second ($n=24$)- or third ($n=12$)-line therapy, or capecitabine in combination with either IFN-γ1b and recombinant IL-2 ($n=12$) or IFN-α ($n=4$). Cm, capecitabine monotherapy; Cc, capecitabine combination therapy; HN-1, IFN-γ1b and recombinant IL-2; alpha-IFN, IFN-α.

Table 2 Toxicity ($n = 54$ patients)

	WHO grade			
	I	II	III	IV
Leukocytopenia	–	1 (1.9%)	–	–
Anemia	3 (5.6%)	1 (1.9%)	1 (1.9%)	–
Thrombocytopenia	–	–	–	–
Hand–foot syndrome	4 (7.4%)	9 (16.7%)	5 (9.3%)	–
Nausea/vomiting	5 (9.3%)	5 (9.3%)	–	–
Diarrhea	–	1 (1.9%)	–	–
Stomatitis	4 (7.4%)	–	1 (1.9%)	–
Infection	1 (1.9%)	1 (1.9%)	–	–

Discussion

Standard first-line treatment for patients with advanced renal cell carcinoma is usually immunotherapy based on IL-2 or IFN-α, reaching response rates of 15–20% [16,17]. Adding 5-FU to the cytokine-based first-line therapy regimens gives overall response rates of 38 and 48.5%, leading to disease stabilization in 73 and 85.6%, respectively [18,19]. However, effective first- or second-line treatment regimens for patients with metastatic renal cell carcinoma are rare [20–23], and other experimental regimens like thalidomide [24,25] monotherapy

or a combination of cytotoxic agents like 5-FU and gemcitabine [23,26] remain poor as well.

Capecitabine, a fluoropyrimidine carbamate, which is converted to 5-FU by a sequential triple enzyme pathway, exhibits a more specific anti-tumor activity than conventional 5-FU, with reduced side-effects [27]. Our study group [13] recently reported results of capecitabine monotherapy in patients with metastatic renal cell carcinoma failing immunotherapy in the second- as well as in the third-line treatment. We could demonstrate disease stabilization of 92.9% in the second- and 77.8% in the third-line treatment. Similar results are reported by Oevermann *et al.* adding capecitabine to standard biological response modifiers in the first-line treatment of 30 patients with advanced renal cell carcinoma. An objective response rate of 34% and a disease stabilization rate of 74% could be demonstrated [14].

In this prospective single-institution clinical phase II trial we report clinical results of patients with metastatic renal cell carcinoma receiving either capecitabine monotherapy after failing immunotherapy in the second- as well as in the third-line treatment, or capecitabine in combination with IFN-γ1b and recombinant IL-2 as first-line therapy or with IFN-α as second-line treatment after failing combined immunotherapy treatment. Patients receiving capecitabine monotherapy revealed a clinical benefit response of 83.4% (30 out of 36 patients) and of 75% (12 out of 16 patients) in the combination treatment. Median TTP was 5 months in the monotherapy treatment group and 4 months in the combination treatment group. Median overall survival was 12 and 7 months, respectively, in these groups.

Capecitabine monotherapy and combination therapy proves to be safe and well tolerated in patients with metastatic renal cell cancer. All side-effects appearing are documented together because of equal frequency and severity of toxicities in the monotherapy and combination treatment. No WHO grade IV toxicities occurred, and the WHO grade III and II toxicities were generally low and were controlled after dose adjustment. None of the patients required hospitalization due to therapy-related side-effects.

In conclusion, capecitabine shows some activity and a favorable toxicity profile in patients with advanced renal cell carcinoma. The present study demonstrates equal response rates as well as equal frequency and severity of toxicities in patients receiving capecitabine monotherapy or combination treatment in indirect comparison. Median TTP and median overall survival time were similar in the monotherapy and the combination treatment group. Therefore capecitabine monotherapy seems to be superior to the combination treatment because of its easier application form and the possibility to apply immunotherapy agents after developing disease progression. In conclusion, capecitabine is a promising candidate for prospective clinical phase III trials in patients with metastatic renal cell cancer as monotherapy, as well as in combination with immunotherapy agents, within controlled clinical trials.

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